

WHAT IS CLAIMED:

1. A method for modulating the differentiation of a mammalian stem cell or progenitor cell comprising differentiating said stem cell or progenitor cell under suitable conditions and in the presence of a compound that inhibits PDE IV activity, wherein said compound is not a polypeptide, peptide, protein, hormone, cytokine, oligonucleotide, or nucleic acid.
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2. The method of claim 1 wherein said stem cell is differentiated into a hematopoietic cell.
3. The method of claim 1 wherein said stem cell is selected from the group 10 consisting of an embryonic stem cell, a placental stem cell, a cord blood stem cell, a peripheral blood stem cell, and a bone marrow stem cell.
4. The method of claim 1, wherein said PDE IV inhibitor is a SelCID™ or a prodrug thereof.
5. The method of claim 1 wherein said differentiating is conducted in cell culture.
- 15 6. The method of claim 1, wherein said differentiating is conducted within an individual.
7. The method of claim 1 wherein the concentration of the compound is from about 0.005 µg/ml to about 5 mg/ml.
8. The method of claim 1 wherein the stem cell is a human stem cell.
- 20 9. A method for modulating the proliferation or differentiation of a mammalian CD34⁺ or CD133⁺ progenitor cell comprising proliferating or differentiating said cell under conditions suitable for proliferation or differentiation and in the presence of a compound that inhibits PDE IV activity, wherein said compound is not a polypeptide, peptide, protein, hormone, cytokine, oligonucleotide, or nucleic acid.
- 25 10. The method of claim 9, wherein said progenitor cell is selected from the group consisting of a CD34⁺ progenitor cell and a CD133⁺ progenitor cell.
11. The method of claim 9, wherein said progenitor cells differentiate into CD34⁺CD38⁻CD33⁺ or CD34⁺CD38⁻CD33⁻ cells.
The method of claim 9, wherein said compound is a SelCID™ or prodrug thereof.
- 30 12. The method of claim 9 wherein said proliferation or differentiation is conducted in cell culture.
13. The method of claim 9, wherein said proliferation or differentiation is conducted within an individual.
14. The method of claim 13, wherein said progenitor cells are cells that have been 35 transplanted into said individual.

15. The method of claim 9, wherein said compound is present in an amount sufficient to cause a detectable difference in said differentiation or proliferation relative to a control.

5 16. The method of claim 9, wherein said CD34⁺ or CD133⁺ progenitor cell has been cryopreserved and thawed prior to said differentiating.

17. A method for expanding a progenitor cell population in a mammalian subject, comprising administering a therapeutically effective amount of CD34⁺ progenitor cells and a compound that inhibits PDE IV activity to said mammalian subject, wherein said compound is not a polypeptide, peptide, protein, hormone, cytokine, oligonucleotide, or nucleic acid

10 18. The method of claim 17 wherein said CD34⁺ progenitor cells are differentiated in said mammalian subject.

19. The method of claim 17 wherein said CD34⁺ progenitor cells are administered to said mammalian subject in a cell preparation that is substantially free of red blood cells.

15 20. The method of claim 17 wherein said CD34⁺ progenitor cells are administered to said mammalian subject in a cell preparation that comprises bone marrow cells, placental cells, or cord blood cells.

21. The method of claim 17 wherein said CD34⁺ progenitor cells are administered to said mammalian subject in conjunction with a carrier.

22. The method of claim 17 wherein said CD34⁺ progenitor cells are CD34⁺CD38⁻CD33⁺ or CD34⁺CD38⁻CD33⁻ progenitor cells.

23. The method of claim 17 wherein said CD34⁺ cell is a CD34⁺CD133⁺ progenitor cell.

24. The method of claim 17 wherein the progenitor cells express incorporated genetic material of interest.

25 25. A pharmaceutical composition comprising a mammalian stem cell and a pharmaceutically-acceptable carrier, wherein said stem cell has been contacted with a compound that inhibits PDE IV activity for a time sufficient to cause modulation of differentiation or proliferation of said stem cell, and wherein said compound is not a polypeptide, peptide, protein, hormone, cytokine, oligonucleotide, or nucleic acid.

30 26. The pharmaceutical composition of claim 25 wherein the stem cell is selected from the group consisting of an embryonic stem cell, a placental stem cell, a cord blood stem cell, a peripheral blood stem cell, and a bone marrow stem cell.

27. The pharmaceutical composition of claim 25 wherein said compound is a SelCIDTM or prodrug thereof.

28. The pharmaceutical composition of claim 25 wherein said contacting step is conducted in cell culture.

29. The pharmaceutical composition of claim 25 wherein the concentration of said compound is from about 0.005 mg/ml to about 5 mg/ml.

5 30. The pharmaceutical composition of claim 25 wherein the stem cell is a human stem cell.

31. The pharmaceutical composition of claim 25 wherein the differentiation is differentiation into a hematopoietic cell.

32. The pharmaceutical composition of claim 25 wherein said hematopoietic cell is a 10 CD34+ or CD38+ hematopoietic cell.

33. The pharmaceutical composition of claim 25 wherein the hematopoietic cell is a CD11b+ cell.

15 34. A pharmaceutical composition comprising isolated cord blood cells and an isolated population of white blood cells, wherein the white blood cells are generated by a method comprising differentiating stem cells under suitable conditions and in the presence of a compound that inhibits PDE IV activity, with the proviso that the compound is not a polypeptide, peptide, protein, hormone, cytokine, oligonucleotide, or nucleic acid, and isolating the white blood cells differentiated thereby.

20 35. The pharmaceutical composition of claim 34 wherein the compound is an imide or amide.

36. The pharmaceutical composition of claim 34 wherein the differentiating step is conducted in cell culture.

25 37. The pharmaceutical composition of claim 34 wherein the concentration of the compound is from about 0.005 µg/ml to about 5 mg/ml.

38. The pharmaceutical composition of claim 34 wherein the stem cell is a human stem cell.

30 39. The pharmaceutical composition of claim 34 wherein the stem cell is a progenitor cell.

40. The pharmaceutical composition of claim 39 wherein the progenitor cell is committed to a specific cell lineage.

41. The pharmaceutical composition of claim 39 wherein the progenitor cell is a hematopoietic progenitor cell.

35 42. A pharmaceutical composition comprising cultured CD34+ or CD133+ progenitor cells and a pharmaceutically-acceptable carrier, wherein said progenitor cells have been contacted within the first six days of culture with a compound that inhibits the

43. The pharmaceutical composition of claim 42 wherein said progenitor cells are collected and cryopreserved after six days of culture.

5 44. The pharmaceutical composition of claim 42 wherein said progenitor cells are CD34⁺CD38⁻CD34⁻ or CD34⁺CD38⁻CD34⁺ cells.

45. The pharmaceutical composition of claim 42 in which said compound is a SelCID™.

10 46. A method of transplanting a mammalian stem cell comprising:

(a) contacting said stem cell with a PDE IV-inhibitory compound to produce a treated stem cell, wherein said contacting is sufficient to modulate the differentiation of said stem cell; and

(b) administering said treated stem cell to an individual.

15 47. The method of claim 46, wherein step (b) comprises administering said treated stem cell in combination with untreated cells.

48. The method of claim 46 wherein the untreated cell is selected from the group consisting of an embryonic stem cell, a placental cell, a cord blood cell, a peripheral blood cell, and a bone marrow cell.

20 49. The method of claim 46, wherein said stem cell has been cryopreserved and thawed prior to said administering.

50. A method of transplanting a mammalian progenitor cell comprising:

(a) contacting said progenitor cell with a PDE VI-inhibitory compound to produce a treated progenitor cell, wherein said contacting is sufficient to modulate the differentiation of said progenitor cell; and

25 (b) administering said treated progenitor cell to an individual.

51. The method of claim 50, wherein step (b) comprises administering said treated progenitor cell in combination with untreated cells.

52. The method of claim 50 wherein the untreated cell is selected from the group consisting of an embryonic stem cell, a placental cell, a cord blood cell, a peripheral blood cell, and a bone marrow cell.

30 53. The method of claim 50, wherein said stem cell has been cryopreserved and thawed prior to said administering.

54. A method of treating an individual experiencing a condition comprising administering to said individual an agent selected from the group consisting of:

- (a) a compound that inhibits PDE IV activity, wherein said compound is not a polypeptide, peptide, protein, hormone, cytokine, oligonucleotide, or nucleic acid;
- (b) a stem cell differentiated in the presence of said compound; and
- (c) a progenitor cell differentiated in the presence of said compound,

5 wherein said agent detectably reduces or ameliorates said condition.

55. The method of claim 54, wherein said condition is selected from the group consisting of inflammation, heart disease, vascular disease, amyotrophic lateral sclerosis, a lysosomal storage disease, and diabetes.

56. The method of claim 54, wherein said agent comprises both a stem cell and

10 compound that inhibits PDE IV activity, wherein said compound is not a polypeptide, peptide, protein, hormone, cytokine, oligonucleotide, or nucleic acid

57. A method of treating an individual comprising administering a therapeutically effective amount of white blood cells to said recipient mammalian subject, wherein said white blood cells are generated by a method comprising differentiating a stem cell under

15 suitable conditions and in the presence of a compound that inhibits PDE IV activity, with the proviso that the compound is not a polypeptide, peptide, protein, hormone, cytokine, oligonucleotide, or nucleic acid.

58. The method of claim 57 wherein the stem cells are differentiated *in vitro*.

59. The method of claim 57 wherein the stem cells are differentiated in a postpartum

20 perfused placenta.

60. The method of claim 57 wherein the white blood cells are administered to the individual in a cell preparation that is substantially free of red blood cells.

61. The method of claim 57 wherein the white blood cells are administered to the individual in a cell preparation which comprises cord blood cells.

25 62. The method of claim 57 wherein the white blood cells are administered to the individual in conjunction with a carrier.

63. The method of claim 57 wherein the white blood cells are administered to treat or repair a defect in the recipient mammalian subject.

64. The method of claim 63 wherein the defect is a hematopoietic or blood cell

30 proliferation defect.

65. The method of claim 63 wherein the hematopoietic or blood cell proliferation defect is neutropenia or leukopenia.

66. The method of claim 63 wherein the white blood cells are administered systemically.

67. The method of claim 63 wherein the white blood cells are administered

intravenously.

68. The method of claim 63 wherein the white blood cells express incorporated

genetic material of interest.

5 69. The method of claim 57 wherein the white blood cells are allogeneic.

70. The method of claim 57 wherein the recipient mammalian subject is human.

10 71. A method of making a pharmaceutical composition, comprising:

(a) contacting CD34⁺ or CD133⁺ progenitor cells with a compound that
inhibits PDE IV activity, wherein said progenitor cells are cultured for six days
under culture conditions that allow proliferation and differentiation of said
progenitor cells;

(b) collecting said cells after six days of culture; and

(c) placing said cells in a pharmaceutically-acceptable carrier.

15 72. The method of claim 71 wherein said contacting is performed on the first day of

culture.

73. The method of claim 71, wherein said contacting is performed at least twice
during said six days of culture.

16 74. The method of claim 71, wherein said compound is a SelCIDTM or a prodrug
thereof.

20 75. The method of claim 71, wherein said progenitor cells have been isolated from
other blood cells prior to said culturing.

76. The method of claim 71, wherein said culture medium additionally contains
GM-CSF and TNF- α .

25 77. The method of claim 74, wherein said SelCIDTM or a prodrug thereof is present
in a concentration of between 0.1 μ M and 10.0 μ M.

78. The method of claim 74 wherein said SelCIDTM or a prodrug thereof is present at
a concentration of 1.0 μ M.

79. The method of claim 74, wherein said cells are cryopreserved after said
collecting.

30 80. A pharmaceutical composition made by the process of claim 74.

81. A method for modulating the differentiation of a CD34⁺ or CD133⁺ progenitor
cell comprising:

(a) providing a population of said progenitor cells under conditions such
that differentiation can occur;

(b) contacting said progenitor cells with a compound, wherein said compound is a PDE IV inhibitor; and

5 (c) differentiating said progenitor cells under conditions suitable for differentiation, wherein said compound is placed in contact with said progenitor cells for at least part of the time said progenitor cells are differentiating.

82. The method of claim 81, wherein in step (b), said contacting is performed at any time between day 0 to day 6 of culture.

83. The method of claim 81, wherein in step (b), said contacting is performed at the start of the culture of said progenitor cells.

10 84. The method of claim 81, wherein in step (b), said contacting is performed after said progenitor cells have proliferated for at least two days.

85. The method of claim 81, wherein in step (b), said contacting is performed after said progenitor cells have proliferated for at least six days.

15 86. The method of claim 81, wherein said progenitor cells are CD34⁺ progenitor cells.

87. The method of claim 81, wherein said progenitor cells differentiate into cells exhibiting cell surface marker characteristics selected from the group consisting of:

- a decrease in CD11c expression relative to a control;
- a decrease in CD38 expression relative to a control;
- 20 a decrease in CD80 expression relative to a control;
- a decrease in CD86 expression relative to a control;
- a decrease in CD1a expression relative to a control;
- a decrease in CD14 expression relative to a control;
- a decrease in CD54^{bright} expression relative to a control;
- 25 a decrease in HLA-DR expression relative to a control;
- an increase in CD15 expression relative to a control;
- an increase in CD33 expression relative to a control;
- an increase in CD54^{dim} expression relative to a control;
- 30 an increase in CD133 expression relative to a control; and
- a combination of any of the above marker characteristics;

wherein said control is a CD34⁺ progenitor cell cultured under the same conditions as said progenitor cell in the absence of said compound.

88. The method of claim 81, wherein said progenitor cells differentiate into CD34⁺CD38⁻CD33⁺ or CD34⁺CD38⁻CD33⁻ cells.

89. The method of claim 81, wherein said PDE IV inhibitor is a SelCID™ or prodrug thereof.

90. A method of producing differentiated cells from CD34⁺ progenitor cells comprising culturing said cells in a culture medium that allows proliferation and differentiation, and contacting said progenitor cells with a SelCID™ or prodrug thereof.

5 91. The method of claim 90, wherein said contacting is performed on the first day of said culturing.

92. The method of claim 90, wherein said contacting takes place at least twice during the first six days of said culturing.

10 93. The method of claim 90, wherein said contacting takes place no earlier than said first day of culturing.

94. The method of claim 90, wherein said differentiated cell is a dendritic cell, a granulocyte, a CD34⁺CD38-CD33⁺ or a CD34⁺CD38-CD33- cell.

15 95. The method of claim 90, wherein said CD34⁺ progenitor cell is a CD34⁺CD133⁺ progenitor cell.

96. The method of claim 90, wherein said differentiated cells are isolated at day 6 of culture.

97. The method of claim 90, wherein said differentiated cells are isolated at day 12 of culture.

20 98. The method of claim 90, wherein said CD34⁺ cells have been isolated from other blood cells prior to said culturing.

99. The method of claim 90, wherein said culture medium additionally contains GM-CSF and TNF- α .

100. The method of claim 90, wherein said SelCID™ or prodrug thereof is 25 present in a concentration of between 0.1 μ M and 10.0 μ M.

101. The method of claim 86 wherein said SelCID™ or prodrug thereof is present at a concentration of 1.0 μ M.